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(54) Title: TOPICAL COMPOSITIONS			
(57) Abstract Topical compositions of urea, useful for the prevention and/or reduction of skin damage caused by ultraviolet radiation.			

TOPICAL COMPOSITIONS

1 This invention relates to topical compositions for
the prevention and/or reduction of skin damage caused by
ultraviolet radiation. In particular this invention
5 relates to the prevention and/or reduction of skin damage
caused by reactive chemical substances generated in the
skin by ultraviolet radiation.

10 The health promoting qualities of sunlight have been
recognized throughout history. However, in recent years,
medical professionals and the lay public both have become
5 aware of the skin diseases and degenerative processes that
occur from prolonged and excessive exposure to ultra-
violet (UV) radiation. Depending on skin types, even
modest exposure can be damaging and dangerous.

15 The mechanisms by which ultraviolet radiation exerts
its adverse effects on the skin are not fully understood.
They are believed to involve absorption of light energy
by skin tissue components to produce very reactive
substances such as free radicals. In particular, they
20 involve the production in the skin tissue of nitroso,
nitrite, and other mediators of undesired skin changes in
sensitive individuals. The potential of nitrites to
react with and damage tissue is well recognized. Recent
experiments in vitro and in vivo have shown the
25 contribution of nitrites to structural alteration of
integumental (skin) structures.

30 Prior art topical compositions-for the prevention of
UV induced skin damage-are essentially sunscreens in that
they absorb light particularly in the ultraviolet wave
lengths associated with skin damage. Even with the broad
spectrum of sunscreen preparations available, ranging
from modest to essentially complete UV blockage, serious
problems of sun damaged skin persist. These sunscreens
are not effective in reducing the formation of free
35 radical substances such as nitrate reduction products in

1 the skin tissue from UV light that do ^s reach the skin. Furthermore, they do not ^hve any effect on the damaging interactions in the skin tissue caused by the free radicals produced.

5 The present invention provides a topical urea composition, for prevention of skin damage due to ultraviolet radiation.

10 Since urea has no ultraviolet light absorbing properties in the skin damaging light wave lengths of 290 to 400 nm, it is not a sunscreen agent. Its skin protective properties are as a neutralizer of damaging active chemical entities. Urea moderates the effects of nitrate reduction products, thus preventing skin damage following ultraviolet radiation.

15 The concentration of urea which may be used in the topical compositions is from about 0.1% to about 40%, preferably from about 1% to about 20% based on the weight of the composition.

20 It is a further embodiment of this invention to use chemical analogs of urea which have functional urea substitutions, in the topical compositions.

25 In a preferred embodiment of this invention urea may be combined with known UV absorbing sun screen agents such as Padimate O (2-ethylhexyl-p-dimethyl amino-benzoate), Oxybenzone (2-hydroxy-4-methoxy benzophenone) and paraaminobenzoic acid (PABA) in topical compositions. This combination of UV absorbing agents and urea free radical neutralizer, provides a superior skin protecting agent to that of the prior art.

30 The UV absorbing agent may be present in the topical composition from about 1% to about 10% by weight of the composition.

35 The topical compositions of this invention are preferably applied to the skin in the form of conventional alcoholic lotions, liquid emulsions, creams, transparent gels, or aerosol sprays.

EXAMPLE

5 The following ingredients were blended to form
 topical cream compositions (A, B, C, D and E) using
 conventional methods.

	<u>Ingredients</u>	Percent w/w				
		<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>	<u>E</u>
10	Mineral Oil	5-20	5-20	5-20	5-20	5-20
	Isopropyl Myristate	0-10	0-10	0-10	0-10	0-10
	Acetylated Lanolin	0-10	0-10	0-10	0-10	0-10
	Alcohol					
	Cetyl Alcohol	1-10	1-10	1-10	1-10	1-10
	Glycerol Mono-					
15	stearate	1-10	1-10	1-10	1-10	1-10
	Tween 80	0-5	0-5	0-5	0-5	0-5
	Methyl Paraffin	0.5	0.5	0.5	0.5	0.5
	Propyl Paraffin	0.2	0.2	0.2	0.2	0.2
	Carbopol 934	0.1	0.1	0.1	0.1	0.1
20	(Polyacrylic acid)					
	Sodium Hydroxide	0-0.1	0-0.1	0-0.1	0-0.1	0-0.1
	Propylene glycol	0-5	0-5	0-5	0-5	0-5
	Urea	15	-	15	-	15
25	X Padimate O	-	1.4-8	1.4-8	-	-
	(2-ethylhexyl-p-di-					
	methyl amino-					
	benzoate)					
	X Oxybenzone	-	-	-	2-6	2-6
	(2-Hydroxy-4-Methoxy					
30	Benzophenone)					
	Water	q.s.	q.s.	q.s.	q.s.	q.s.
	<hr/> Total	100	100	100	100	100

1 In a study of ultraviolet light induced acute and
chronic actinic damage, it was found that the urea
compositions of this invention (e.g., compositions A, C
and E) provided a significant degree of protection
5 against acute sunburn damage in hairless mouse skin as
compared with placebo compositions. Using SK-1 hairless
mice, observations were made of erythema responses under
blinded conditions. There were striking differences in H
10 and E stained tissue sections taken from the reaction
sites. The skin damage in placebo treated sites was two
to three times greater than the urea composition treated
sites, based upon thickness of the epidermis, the number
of sunburn cells noted, and the dermal inflammatory
changes.

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1 **WHAT IS CLAIMED IS:**

1. A method for the prevention and/or reduction of skin damage caused by ultraviolet radiation which comprises topically applying a composition of a
- 5 therapeutically effective amount of urea in a pharmaceutically acceptable carrier to the skin of an individual in need of such skin treatment.
- 10 2. The method according to claim 1 wherein the amount of urea is from about 0.1 to about 40 percent based on the weight of the composition.
- 15 3. The method according to claim 2 wherein the amount of urea is from 1 to about 20 percent.
- 20 4. The method according to claim 1 wherein an ultraviolet radiation absorbing agent is present in the composition.
- 25 5. The method according to claim 4 wherein the ultraviolet radiation absorbing agent is 2-ethylhexyl-p-dimethyl aminobenzoate, 2-hydroxy-4-methoxy benzophenone, or para-aminobenzoic acid.
- 30 6. The method according to claim 5 wherein the amount of ultraviolet absorbing agent is from about 1 to about 10 percent based on the weight of the composition.
- 35 7. A composition for the prevention and/or reduction of skin damage caused by ultraviolet radiation which comprises a therapeutically effective amount of urea and a therapeutically effective amount of an ultraviolet radiation absorbing agent.
- 40 8. The composition according to claim 7 wherein the ultraviolet radiation absorbing agent is 2-ethylhexyl-p-dimethyl aminobenzoate, 2-hydroxy-4-methoxy benzophenone, or para-aminobenzoic acid.
- 45 9. The composition according to claim 7 wherein the amount of urea is from about 0.1 to about 40 percent, and the ultraviolet radiation absorbing agent is from about 1 to about 10 percent, based on the weight of the composition.

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1 10. The composition according to claim 7 wherein
the amount of urea is from about 1 to about 20 percent.

5 11. The composition according to claim 8 wherein
the amount of ultraviolet absorbing agent is from about
1-10 percent based on the weight of the composition.

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INTERNATIONAL SEARCH REP RT

International Application No

PCT/US85/01066

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC
 INT. Cl. (4) A61K 7/42; A61K 7/44
 U.S. Cl 424/59; 424/60

II. FIELDS SEARCHED

Classification System	Minimum Documentation Searched *	Classification Symbols
U.S.	424/59, 60	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X	DE, A, 1,767,165, Joos, 09 September, 1971, Example 6	1 to 11
X	DE, A, 2,703,185, Moller et al, 10 August 1978, page 16, lines 27 to 34	1 to 11
X	DE, A, 2,706,782, Kaplan et al, 01 September 1977, page 7, lines 5 to 22	1 to 11
X	N. The Principles and Practice of Modern Cosmetics, issued March, 1963, Vol. 2 R. G. Harry, See pages 520 to 523	1 to 11
X	N. Handbook of Nonprescription Drugs, issued 1977, American Pharmaceutical Association, See pages 280 to 287, 324 to 328 and 336-338	1 to 11

* Special categories of cited documents: ¹⁵
 "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the International filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search *

02 August 1985

Date of Mailing of this International Search Report *

14 AUG 1985

International Searching Authority *

ISA/US

Signature of Authorized Officer ²⁰

Dale R. Ore